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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,883	04/18/2005	Michel Christian Morre	BKR-110T	9491

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EXAMINER	
XIE, XIAOZHEN	
ART UNIT	**PAPER NUMBER**
1646	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,883	MORRE ET AL.	
	Examiner	Art Unit	
	Xiaozhen Xie	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-110* is/are pending in the application.

4a) Of the above claim(s) *59,60 and 86-110* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-58 and 61-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 February 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20050202*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *seq. alignment*.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The Information Disclosure Statement (IDS) filed 2 February 2005 has been entered. . Applicant's amendment of the specification filed 2 February 2005 has been entered.

Election/Restrictions

Applicant's election with traverse of Group I, claims 56-85, and species election for: A) the amino acid sequence of SEQ ID NO: 2; B) a hematopoietic cell growth factor selected from SCF, G-CSF and GM-CSF; C) a cytokine selected from IL-12; D) an antigen derived from the hepatitis virus A, B, C or E; and E) a nucleic acid molecule comprising SEQ ID NO: 1, in the response received 15 June 2007, is acknowledged.

The traversal is on the ground that Cosenza et al., while naming the claimed conformer, indicated that the actual IL-7 conformer produced and characterized in the reference contained three disulfide bridges at different positions (Cys3-142, Cys35-130 and Cys48-93). Applicant argues that while Cosenza et al. mention the instant claimed conformer in Fig. 3B, it is only referred to as the 1996 Kroemer et al. hypothesis. Applicant argues that Cosenza et al. do not teach the production of the claimed conformer, and explain that they do not believe that this conformer exists in view of the mass spectrophotometric data. Applicant argues that the present inventors have shown that the claimed IL-7 conformer is the preferred conformer for therapeutic use and the

major molecule species within the claimed IL-7 drug substance, thus providing a significant contribution over the prior art.

Applicant's arguments have been fully considered but have not been found to be persuasive.

The Cosenza et al. reference specifically describes the structure for an IL-7 molecule comprising the following three disulfide bridges: Cys:1-4 (Cys2-Cys92); 2-5 (Cys34-Cys129) and 3-6 (Cys47-Cys141), even through it is referring to the 1996 Kroemer et al. reference (Protein Engineering, 1996, 9(6):493-498). Claim 1 is directed to an IL-7 drug substance comprising an IL-7 conformer which has these three disulfide bridges, rather than a method for producing the molecule. Cosenza et al. teach an IL-7 conformer that is identical to the structure of the instant invention, and meets the limitations of claim 1. Thus the limitations of Group I lack novelty or inventive step and do not make a contribution over the prior art. Since the 1st claimed invention has no special technical feature, it cannot share a special technical feature with the other claimed inventions.

The requirement is still deemed proper and is therefore made FINAL. Claims 1-55 are cancelled. Claims 56-110 are pending. Claims 86-110 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Claims 56-85 are under examination to the extent they read on the elected species. Claims 56-58 and 61-85 read on the elected species.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Drawings

The drawings (Figures 9, 12 and 16) are objected to under 37 CFR 1.83(a) because they fail to show details as described in the specification. Figures 9, 12 and 16 are not legible. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application

must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

Claim 66 is objected to because of the following informalities:

Claim 66 recites "an other IL-7 conformer", which appears to be "another IL-7 conformer" or "other IL-7 conformers".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 56 and 61-85 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to an IL-7 drug substance comprising an IL-7 conformer that comprises three disulfide bridges: Cys:1-4 (Cys2-Cys92); 2-5 (Cys34-Cys129) and 3-6 (cya47-Cys141), wherein the total amount by weight of IL-7 is at least 98% and the

drug substance is substantially free of IL-7 variants or product related impurities. What applicant has described in the specification is a human IL-7 conformer comprising the amino acid sequence of SEQ ID NO: 2, that has three disulfide bridges at the positions Cys:1-4 (Cys2-Cys92), 2-5 (Cys34-Cys129) and 3-6 (cya47-Cys141). Applicant has not described other IL-7 conformers with the recited disulfide bridges. While IL-7 is well known in the art, IL-7 from different species, e.g., human, mouse and bovine, has been isolated and the sequences have been identified, however, except for human IL-7, other IL-7 molecules do not have cysteine residues at the recited positions (Kroemer, et al., Protein Engineering, 1996, 9(6):493-498; see pp. 494, Fig. 1). Therefore, the specification does not disclose a representative number of species of IL-7 conformers commensurate with the scope of the genus of IL-7 conformer recited in claim 1 (i.e., an IL-7 conformer that comprises three disulfide bridges: Cys:1-4 (Cys2-Cys92); 2-5 (Cys34-Cys129) and 3-6 (cya47-Cys141). Thus, the claims encompass a genus of molecules, which vary substantially in composition, and could have very different structural and functional characteristics from the IL-7 conformer that Applicant has disclosed.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making of the claimed product, or any combination thereof. In this case, there is not even identification of any particular portion

of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of peptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that is part of the invention and reference to a method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a human IL-7 conformer comprising the amino acid sequence of SEQ ID NO: 2, that has three disulfide bridges at the positions Cys:1-4 (Cys2-Cys92),

2-5 (Cys34-Cys129) and 3-6 (cya47-Cys141), but not the full scope of the claimed IL-7 conformers are adequately described in the disclosure.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 71, 80 and 85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 80, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 71 and 85 are indefinite for the recitations of "a pH range comprised between 5 to 7.5" (claim 71), and "the effective amount of the drug substance is comprised between about 3 to 300 μg/kg/day" (claim 85). Since "comprising" is an open language, it is unclear if the claim is intended to encompass pH between 5-7.5, and the drug dosage between about 3 to 300 μg/kg/day, or beyond the ranges. The metes and bounds of the limitations cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 56-58, 61, 66, 67 and 81-84 are rejected under 35 U.S.C. 102(b) as being anticipated by Cosenza et al. (Prot. Sci., 2000, 9:916-926, reference provided in the previous office action).

The claims are directed to a an IL-7 drug substance comprising an IL-7 conformer that comprises three disulfide bridges: Cys:1-4 (Cys2-Cys92); 2-5 (Cys34-Cys129) and 3-6 (cya47-Cys141), wherein the total amount by weight of IL-7 is at least 98% or at least 99.5 %, and the drug substance is substantially free of IL-7 variants or product related impurities (claims 56, 66, 67); wherein the IL-7 conformer is a rh-IL-7 conformer and comprises the amino acid sequence of SEQ ID NO: 2 (claims 57, 58); wherein the IL-7 conformer is not glycosylated (claim 61); wherein the pharmaceutical composition is for administration to a human patient for stimulating B or T lymphocyte development or proliferation, to reduce opportunistic infections in immunodeficient patients, and to prolong lymphopoiesis stimulation (claim 81-84).

Cosenza et al. teach a 3-D structure for a recombinant human IL-7 comprising the following three disulfide bridges: Cys:1-4 (Cys2-Cys92); 2-5 (Cys34-Cys129) and 3-6 (Cys47-Cys141) (pp. 919, Fig. 3B). The 3-D structural model is constructed for the structure of a pure molecule (e.g., IL-7 in a crystal). The rh-IL-7 comprises the amino acid sequence of SEQ ID NO: 2 of the instant invention (see alignment). Cosenza et al. teach that IL-7 is expressed from *E. coli* (non-glycosylated), and refolded and purified (e.g., through HPLC sizing) (substantially free of IL-7 variants or product-related impurities) (see section Materials and Methods, pp. 925, left column). Cosenza et al.

teach that IL-7 can stimulate pre-B-cell and mature T-cell proliferation, can induce LAK cells and cytolytic T-cells, and may have therapeutic applications in cancer immune therapy and treatment of immune deficiency disease (pp. 917, left column, 1st paragraph). Therefore, Cosenza et al. anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 62, 68-80, 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cosenza et al., in view of Namen et al. (U.S. Patent No: 4,965,195, issued on 23 October 1990), and further in view of Ho et al. (U.S. Patent No: 5,714,141, issued on 3 February 1998).

Cosenza et al. teach as set forth above. Cosenza et al., however, do not teach that the IL-7 conformer is glycosylated (claim 62); nor teach a pharmaceutical composition comprising the IL-7 drug substance and one or more pharmaceutically acceptable carriers (claim 68), wherein the carrier is, e.g., sucrose, and is contained in an isotonic buffer, e.g., a sodium citrate buffer with a pH 5-7.5 (claims 69-72); wherein the pharmaceutical composition is in a lyophilized form (claim 73), comprises a surfactant or a protein (claim 74); wherein the pharmaceutical composition further comprises a hematopoietic cell growth factor, (e.g., SCF, G-CSF, GM-SCF), a cytokine

(e.g., IL-2), an antigen derived from, e.g., a Hepatitis A. B. C. or E virus, and/or an adjuvant selected from any substance facilitating the immunogeneicity of an antigen and able to induce a Th1-type immune response, such as monophosphoryl lipid A (claims 75-80); wherein the effective amount of the pharmaceutical composition is between 3-300 μg/kg/day (claim 85).

The '195 patent teaches expressing IL-7 in mammalian cell culture systems (glycosylated protein) (column 9, line 66 through column 10, line 27). The '195 patent teaches the therapeutic compositions comprising IL-7 and physiologically acceptable carriers, excipients or diluents. The '195 patent teaches that neutral buffered saline mixed with conspecific serum album are exemplary appropriate diluents; and preferably, the product is formulated as a lyophilizate using appropriate excipient solutions (e.g., sucrose) as diluents. The '195 patent teaches that IL-7 can be used in conjunction or admixture with other lymphokines, e.g., IL-2, G-CSF, or GM-CSF. The '195 patent teaches that the dosages of 10 ng to 100 μg/kg/day can be expected to induce a biological effect (column 16, lines 5-17). The '195 patent teaches addition of adjuvants, e.g., plant lectin concanavalin A (ConA) or phytohemaglutinin (PHA), to augment the response of IL-7 as a T-cell mitogen (column 31,line 1-57).

The '141 patent teaches using IL-7 to improve the potency of a vaccine (column 3, lines 63-67), e.g., a recombinant hepatitis B vaccine (column 4, line 67 through column 5, line 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Cosenza et al., with those of

the '195 patent and the '141 patent, to prepare an IL-7 conformer from a mammalian expression system and use the protein to make pharmaceutical compositions. One of ordinary skill in the art would have been motivated to combine the teachings, because Cosenza et al., teach a rh-IL-7 conformer that can stimulate pre-B-cell and mature T-cell proliferation and may have therapeutic applications in cancer immune therapy and treatment of immune deficiency disease, the '195 patent teaches using the IL-7 protein to make pharmaceutical compositions which comprise the components as recite in the claims, and the '141 patent further teaches combining IL-7 with a recombinant hepatitis B vaccine to improve the potency of the vaccine. Therefore, the combined teachings provide a reasonable expectation of successfully making IL-7 pharmaceutical compositions.

Claims 63-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cosenza et al., in view of Goldschneiser et al. (Pub. No.: US 2002/0058791 A1, which has a priority filing date on 30 March 2000), and further in view of Goeddel et al. (U. S. Patent No.: 5,223,408, issued on 29 June 1993).

Cosenza et al. teach as set forth above. Cosenza et al., however, do not teach that the IL-7 conformer is associated to HGF as a heterodimer (claim 63), or is functionally associated with IgG1-Fc or human arum albumin (HAS) (claims 64, 65).

Goldschneiser et al. teach a hybrid cytokine of IL-7 and HGF β-chain as a pre-pro-B Cell Growth Stimulating Factor (PPBSF) that exhibit unique lymphopoietic

properties [0002][0012]. Goldschneiser et al. teach that the IL-7/HGFβ can be joined by disulfide-bridges produced by the two polypeptides (heterodimer) [0019].

The '408 patent teaches conjugating an immunogenic polypeptide, e.g., IL-7 (column 6, line 36), with Ig Fc or albumin to increase half-life (column 19, lines 33-43).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Cosenza et al., with those of Goldschneiser et al. and the '408 patent, to conjugate or link the IL-7 conformer with HGF, or with IgG1-Fc or HAS. One of ordinary skill in the art would have been motivated to combine the teachings, because Cosenza et al., teach a rh-IL-7 conformer that can stimulate pre-B-cell and mature T-cell proliferation and may have therapeutic applications in cancer immune therapy and treatment of immune deficiency disease, Goldschneiser et al. teach that a hybrid cytokine of IL-7/HGFβ exhibits unique lymphopoietic properties, and the '408 patent teaches that conjugating IL-7 with Ig Fc or albumin can increase half-life. Therefore, the combined teachings provide a reasonable expectation of successfully making an IL-7 drug.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph. D.
August 27, 2007

Eileen B. O'Hara

EILEEN B. O'HARA
PRIMARY EXAMINER